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TITLE: Breast Cancer Risk in Relation to Serum IGF-1, IGFBP-3, and Their Genetic Determinants: A Study Within the European Prospective Into Cancer (EPIC)

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13. ABSTRACT (Maximum 200 Words)

Purpose and scope: We are conducting a large case-control study nested within a prospective cohort, to estimate relative risks of breast cancer by serum levels of IGF-I and IGFBP-3, and to examine associations of polymorphisms in 15 candidate genes with levels of IGF-I, IGFBP-3, and cancer risk.

Progress report: in the first two years of this project, 1084 breast cancer cases and 2116 control subjects were included in the study, and measurements of IGF-I and IGFBP-3 were (practically) completed. A first series of 23 SNPs were typed for all case and control subjects, and typing of 18 additional SNPs is ongoing.

Major findings: Elevated serum IGF-I shows a moderate increase in breast cancer risk among postmenopausal women. Preliminary analyses also show significant associations of a number of SNPs and haplotypes with IGF-I, IGFBP-3, or breast cancer risk.

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INTRODUCTION

IGF-I is a central hormone in the regulation of anabolic (growth) processes as a function of available energy and elementary substrates (e.g., essential amino acids), and has strongly mitogenic and anti-apoptotic activities. Results from *in vitro* studies and animal experiments show that, in excess, the anabolic signals by IGF-I can promote the development of tumors at various organ sites, and recent epidemiological studies have shown an increased breast cancer risk in women with elevated serum IGF-I, or with elevated levels of IGF-I for given levels of IGFBP-3, the major plasmatic IGF-binding protein.

While nutritional status is one important determinant of circulating IGF-I levels (Kaaks & Lukanova, 2001), heritability studies have shown that, in well-nourished populations, a large part (40-60 %) of variation in IGF-I is (co)determined by genetic factors (Harrela et al., 1996; Hong et al. 1996; Verhaeghe et al., 1996). To increase understanding of what are the major determinants of IGF-I levels, as well as cancer risk, we conduct a study with the following objectives:

1. Confirm that elevated prediagnostic serum levels of IGF-I increase breast cancer risk, especially in premenopausal women;

2. Describe exhaustively existing polymorphisms, allele frequencies and haplotypes in 15 selected genes related to the secretion of growth hormone, and hence to the synthesis of IGF-I and IGFBP-3; and

3. Examine whether these genetic polymorphisms are related to significant increases or decreases in circulating levels of IGF-I and IGFBP-3, as well as in breast cancer risk.

Our project is a large case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC), using prediagnostic blood (serum and DNA) samples collected during 1992-1998, from 233,800 women in western Europe.

As mentioned in our original application, the study was planned in four parts:

1. A case-control study (about 1000 cases and 1000 controls) nested in a prospective cohort, to estimate the associations of serum IGF-I and IGFBP-3 levels with breast cancer risk;

2. Preparation of an exhaustive catalogue of polymorphisms and haplotypes in the 15 selected candidate genes, and a ("phase-1") association study on a subset of 400 controls to identify genotypes that have a minimum level of association with serum of IGF-I and IGFBP-3;

3. A nested case-control study, to estimate relative risks of breast cancer in relation only to those genotypes selected in phase-1;

4. A ("phase-2") study of associations of these selected genotypes with IGF-I and IGFBP-3, in all cases and controls.

BODY

For **Year 1**, our workplan (as in the "Statement of Work" section of our application), was as follows:

1. Selection of cases and controls, using the established eligibility and matching criteria, and extraction of case-control data sets with relevant information from questionnaires and anthropometry: **Task 1, months 1-2.**

2. Retrieval of serum and buffy coat samples from the central EPIC storage facility; assembly of the serum samples into batches of matched case-control sets for immunoassays; assembly of the buffy-coat samples into batches for DNA extraction: **Task 2, months 2-4.**

3. Assays of IGF-I and IGFBP-3 serum of breast cancer cases (n = 1000) and controls (n = 1000): **Task 3, months 7-12.**

4. DNA extraction for all 2000 cases and controls: **Task 5, months 1-12.**

5. Preparation of an exhaustive catalog of polymorphisms by searching the literature, and by DHPLC analysis of DNA from a subset of 200 subjects: **Task 6: months 1-12.**

As described in our previous report (Year 1), we achieved most of these goals in Year 1, whereas for some other tasks we were in advance of our planned schedule. The following list provides a quick recapitulation of key accomplishments in Year 1:

a) *Case-control selection, DNA extraction, and growth factor measurements*:
   - An almost complete selection of breast cancer cases (n=810) and control subjects (n=1620) within the EPIC cohorts, for the nested case-control study on serum IGF-I, IGFBP-3 and breast cancer risk;
   - Measurement of IGF-I and IGFBP-3 for these cases and controls;
   - DNA extraction for these cases and controls;

b) *Preparation of SNP genotyping tools*:
   - Identification of a comprehensive catalogue of >120 (possible) single nucleotide polymorphisms (SNPs) in all candidate genes included in the present study;
   - Preparation of a DNA genotyping chip, for 78 of these polymorphisms that had confirmation of being true polymorphisms;

c) *Preliminary genotyping study*:
   - A first descriptive study of SNP and haplotype frequencies for all candidate genes, in a population of 477 subjects (women plus men); and
   - A preliminary analysis of associations of SNPs and circulating levels of IGF-I and IGFBP-3 (corresponds to **Task 7**, originally planned for Year 2);
   - Selection of a first series of 23 SNPs to be typed in the full case-control study, using the Taqman assay.

During **Year 2**, we completed some of the tasks originally planned for Year 1. In particular, we included 274 cases of breast cancer and 496 control subjects, for whom questionnaire information available in 2002 did not allow proper control matching (this information arrived during 2002). Thus, total numbers of breast cancer cases and control subjects were brought to 1084 and 2116, respectively.

For these additional study subjects, DNA was extracted from their stored buffy coat specimens, and additional serum measurements of IGF-I were performed. For IGFBP-3, measurements were delayed because of technical difficulties with the (commercial) assay, due to complications at the manufacturing site (DSL, TX, USA). In collaboration with the company, these problems have now been solved, and completion of the IGFBP-3 assays is scheduled for September-October 2003.

Tasks planned for Years 2 and 3 ("Statement of Work" section of our study proposal) were:

6. Statistical analysis of the nested case-control study, relating breast cancer risk to prediagnostic serum levels of IGF-I and IGFBP-3 (**Task 4, months 13-24**);

7. Complete genotyping of a subset of 200 breast cancer cases and 200 control subjects; Statistical analysis of phase-1 association study, relating genotypes to serum concentrations of IGF-I and IGFBP-3 (**Task 7; months 12-24**); and

8. Genotyping of the remaining 1600 cases and controls, for a limited set of polymorphisms, selected in phase 1;

Statistical analysis of associations between polymorphisms, serum levels of IGF-I and IGFBP-3, and breast cancer risk; Writing of reports (**Task 8; months 24-36**).

All of the goals up to the end of Year 2, and much of the goals for Year 3, have been met:

(a) Statistical analysis of breast cancer risk in relation to prediagnostic serum levels of IGF-I and IGFBP-3 (**Task 4**):

Although IGFBP-3 measurements are not complete yet (see above), we performed extensive statistical analyses of the relationships of breast cancer risk with serum IGF-I and IGFBP-3 concentrations. These analyses showed no clear relationship of breast cancer risk with IGF-I among women who were premenopausal at the time of blood donation, contrary to findings from some previous cohort studies. Among postmenopausal women, however, there was a moderate association of risk with IGF-I (relative risk of about 1.5 between the extreme quintiles of the IGF-I exposure distribution).

(b) Further SNP genotyping of breast cancer cases and control subjects (**Task 8**):

For all 1084 breast cases and 2116 controls included in th nested case-control study, a first series of 23 SNPs were typed by Taqman. For an additional number of SNPs, genotyping assays by the Taqman technique did not work (a normal observation with this type of assay); for these, we are currently trying to set up alterantive assays (e.g., "Amplifluor"). For yet another set of SNPs, our DNA chip initially used for genotyping in a smaller subset of individuals (total of 78 SNPs) did not give valid

results, and we were thus unable not confirm whether or not polymorphic alleles were prevalent enough to make their measurement worthwhile. For this latter subset, we have now decided to type all of these SNPs by Taqman or the Amplifluor technique. In total, some 18 SNPs remain to be typed for all case and control subjects, which will bring the total number of SNPs typed to 41. This total number of assays (SNPs) is considerably larger than that foreseen in our original study proposal; however, genotyping of this increased number largely has become possible due to the progressive reductions in genotyping reagent costs.

(c) Statistical analysis of SNP / haplotype associations with IGF-I and IGFBP-3 (**Tasks 7 and 8**):

In Year 1, performed preliminary statistical analyses were performed to examine possible associations of SNPs and their haplotypes with serum concentrations of IGF-I and IGFBP-3, within a first series of 477 subjects (see our previous report).
During Year 2, we re-analysed our much more extensive data, from all 1084 breast cancer cases and 2116 controls, using the same methods as in Year 1.
Analyses were performed with a variety of statistical models, of increasing completeness and complexity:

- *at the level of individual SNP loci*: associations of alleles with IGF-I and IGFBP-3 concentrations were estimated under assumption of dominance, codominance, or recessiveness of alleles.
- *at the level of full gene loci*: individuals' most likely haplotypes were estimated, and individuals' haplotype combinations (of the two chromosomes) were associated with IGF-I and IGFBP-3 levels; in further analysis, haplotypes were transformed into SNP genotypes sorted by parental phase, and generalized linear models (GLM) were used to relate phenotype (IGF-I, IGFBP-3) to these phased genotype variables, plus their possible interaction terms within a gene (following an approach described by Cordell and Clayton, 2001).

During *Year 2*, we have also been working further on refinements of the statistical analysis procedures, implementing several new procedures (programmed in SAS), and testing different existing programs for estimation of haplotypes ('Arlequin'; 'PHASE'; 'SAS-Genetics'; TagSNP). A final analysis will be performed when genotyping of all 41 SNPs will be completed (planned to be complete by the end of 2003). Only after completion will it be possible to estimate full haplotypic variation at gene loci, and to perform definitive analyses.

Preliminary analyses of Year 1 suggested that up to some 20% of the total between-subject variation in IGF-I levels might be explained by measured genetic polymorphisms. This percentage was most likely overestimated, due to a comparatively small study size and over fitting of statistical models. Our current analyses, based on much larger numbers of observations, show smaller, but probably more realistic effects of SNPs and/or haplotypes on serum IGF-I and IGFBP-3 levels. Amongst the most significant associations was the relationship of IGFBP-3 levels with SNPs in the IGFBP-3 gene, which has also been observed in other studies (Jernström et al., 2001).

(d) Statistical analysis of SNP / haplotype associations with breast cancer risk (**Task 8**):

Preliminary statistical analyses have been performed, using logistic regression models to relate breast cancer risk to SNP genotypes as well as to haplotypes. The analytical strategy is similar to that for the analysis in relation to serum IGF-I and IGFBP-3 concentrations (described above). In addition, we have implemented a series of models to estimate haplotype relative risks, for a haplotype 'dosage' estimated as posterior probability for each of the possible haplotypes given SNP genotypes (following methods described by Stram et al., 2003).

A definitive statistical analysis of breast cancer risk in relation to SNP genotypes and, especially, haplotypes will be possible only after completion of genotyping for all 41 SNPs (by the end of 2003).

KEY RESEARCH ACCOMPLISHMENTS

Key research accomplishments in Year 2 were:

- Inclusion in the study of 274 additional breast cancer cases and 496 additional control subjects, bringing the total number of cases and controls to 1084 and 2116, respectively;
- DNA extraction and genotyping of a first series of 23 SNPs, for all cases and controls;
- IGF-I measurements for all cases and controls; nearly complete measurements of IGFBP-3.
- Extensive preliminary statistical analyses of associations between breast cancer risk, prediagnostic serum levels of IGF-I and IGFBP-3, and SNP and haplotype data; Preparation of programs and SAS macros for all analytical steps, ready to be implemented when all laboratory analyses will be completed.

PLAN FOR YEAR 3

Plans for Year 3 are as follows:

- Completion of genotyping of the 18 additional SNPs identified, and selected for the study;
- A definitive statistical analysis of the complete SNP genotype and haplotype data, in relation to serum IGF-I and IGFBP-3, as well as breast cancer risk;
- Preparation of articles, to report all major findings in scientific journals.

REPORTABLE OUTCOMES

None, so far. First drafts of articles are in preparation; these will be finalized after completion of all laboratory assays for genotypes and IGFBP-3, and definitive statistical analysis.

CONCLUSIONS

Our study is ahead of schedule, and actually has been expanded to include a larger number of SNP assays than initially foreseen (made possible because of decreasing genotyping costs). Results so far do indicate a number of associations of IGF-I, IGFBP-3 and breast cancer risk with SNP genotypes and/or haplotypes for full gene loci. The overall proportion of between-person variance in circulating levels of IGF-I and IGFBP-3 explained by the genetic polymorphisms is modest, however, but is still based on rather incomplete SNP and haplotype data.

Elevated serum IGF-I concentrations show a modest increase in breast cancer risk, but only among postmenopausal women.

Final statistical analyses of associations between breast cancer risk in relation to IGF-I, IGFBP-3, and genetic variants will be performed in Year 3, after the completion of the IGFBP-3 assays and additional SNP genotyping.

REFERENCES

Cordell H & Clayton D. (2002) A unified stepwise regression procedure for evaluating the relative effects of polymorphisms within a gene using case/control or family data: application to HLA in type 1 diabetes. Am J Hum Genet.70:124-41.

Harrela M, Koistinen H, Kaprio J, Lehtovirta M, Tuomilehto J, Eriksson J, Toivanen L, Koskenvuo M, Leinonen P, Koistinen R, Seppala M. (1996) Genetic and environmental components of interindividual variation in circulating levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3. J Clin Invest. 98:2612-5.

Hong Y, Pedersen NL, Brismar K, Hall K, de Faire U. (1996) Quantitative genetic analyses of insulin-like growth factor I (IGF-I), IGF-binding protein-1, and insulin levels in middle-aged and elderly twins. J Clin Endocrinol Metab. 81:1791-7.

Jernstrom H, Deal C, Wilkin F, Chu W, Tao Y, Majeed N, Hudson T, Narod SA, Pollak M., 2001 Genetic and nongenetic factors associated with variation of plasma levels of insulin-like growth factor-I and insulin-like growth factor-binding protein-3 in healthy premenopausal women. Cancer Epidemiol Biomarkers Prev. 10:377-84.

Kaaks R & Lukanova A. (2001) Energy balance and cancer: the role of insulin and IGF-I. Proc Nutr Soc , 60: 91-106.

Schneider, Roessli & Excoffier (2000) Arlequin: A software for population genetics data analysis. Ver 2.000. Genetics and Biometry Lab, Dept. of Anthropology, University of Geneva.

Stram DO, Haiman CA, Hirschhorn JN, Altshuler D, Kolonel LN, Henderson BE, Pike MC. (2003) Choosing haplotype-tagging SNPS based on unphased genotype data using a preliminary sample of unrelated subjects with an example from the Multiethnic Cohort Study. Hum Hered. 55:27-36.

Verhaeghe J, Loos R, Vlietinck R, Herck EV, van Bree R, Schutter AM. (1996) C-peptide, insulin-like growth factors I and II, and insulin-like growth factor binding protein-1 in cord serum of twins: genetic versus environmental regulation. Am J Obstet Gynecol. 175:1180-8.

APPENDICES

Tables with preliminary results from statistical analyses

Figure 1. Relative risk of breast cancer by quintiles of growth hormone levels

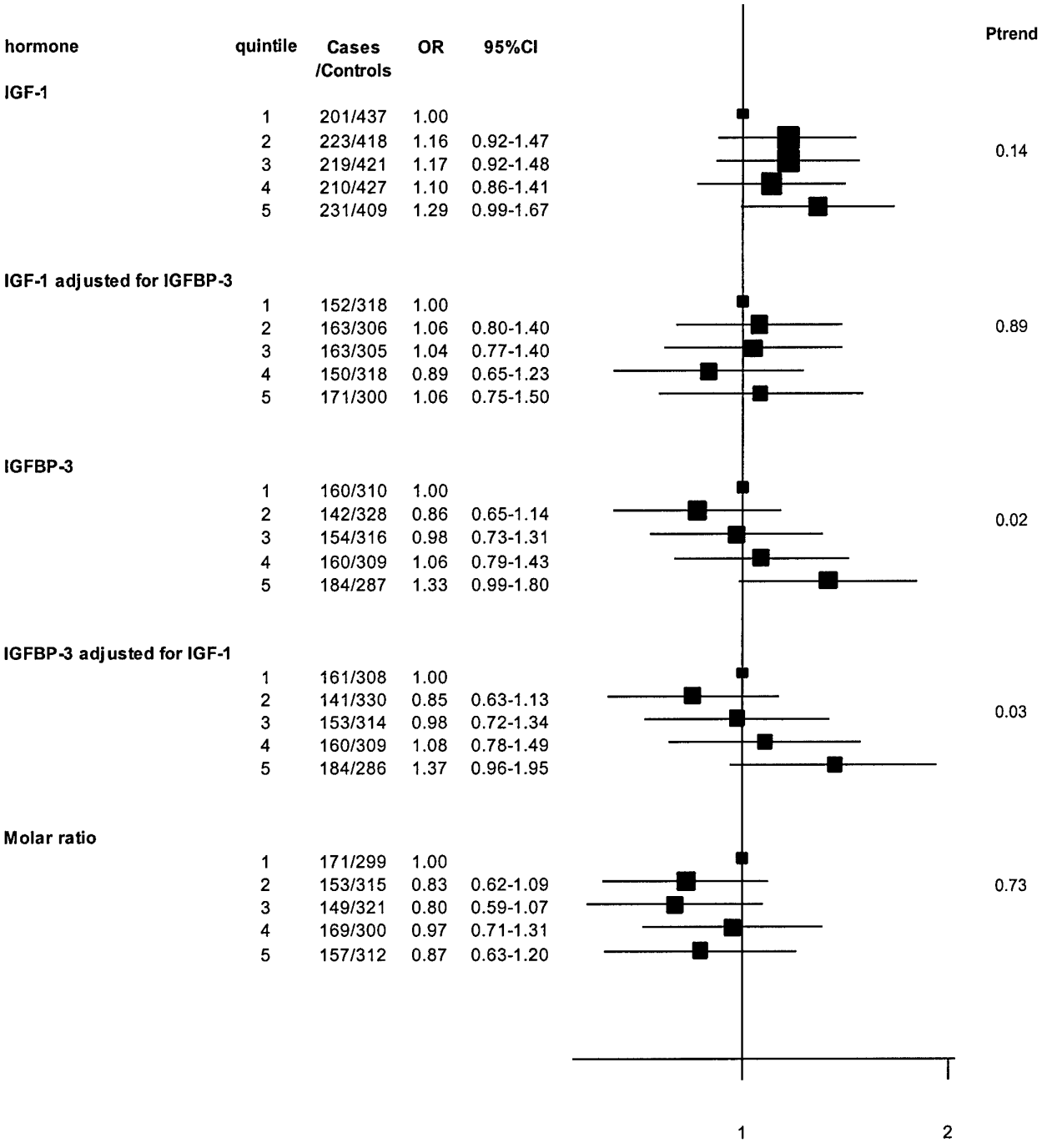

Figure 2. Relative risk of breast cancer among premenopausal women by quintiles of growth hormone levels

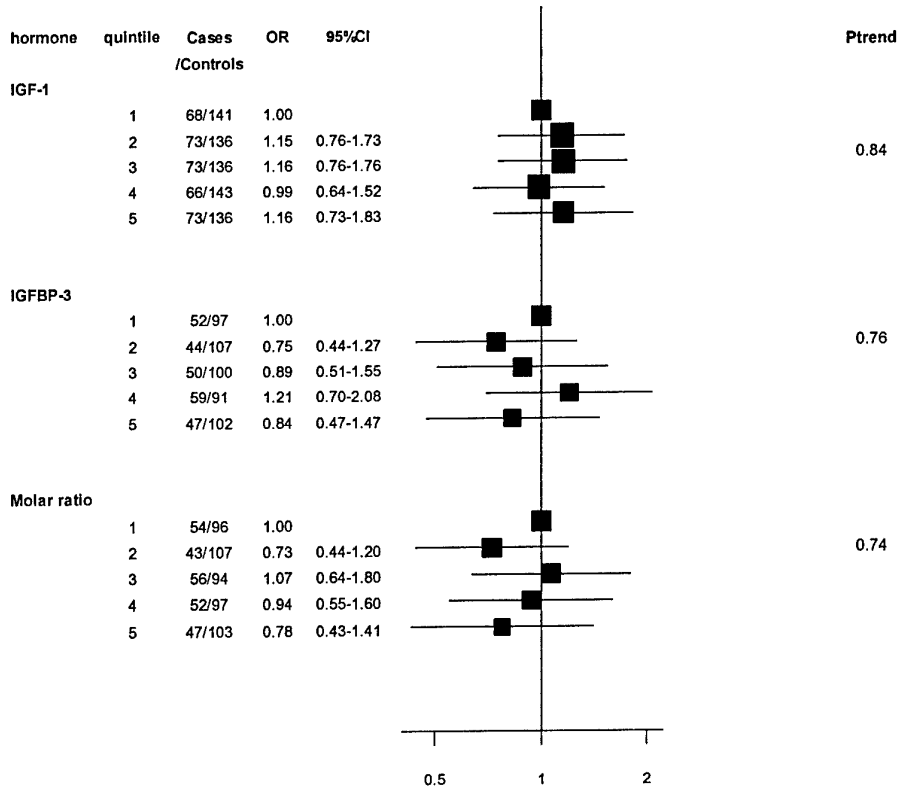

Figure 3. Relative risk of breast cancer among postmenopausal women by quintiles of growth hormone levels

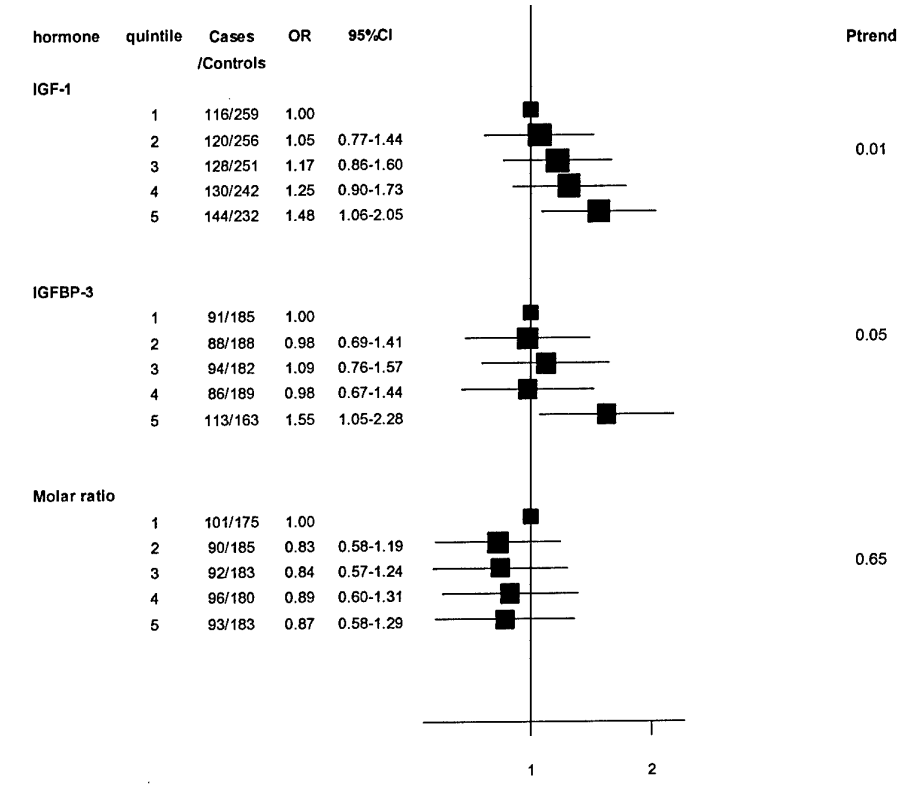

Figure 4. Relative risk of breast cancer among women younger than 50 at diagnosis at diagnosis by quintiles of growth hormone levels

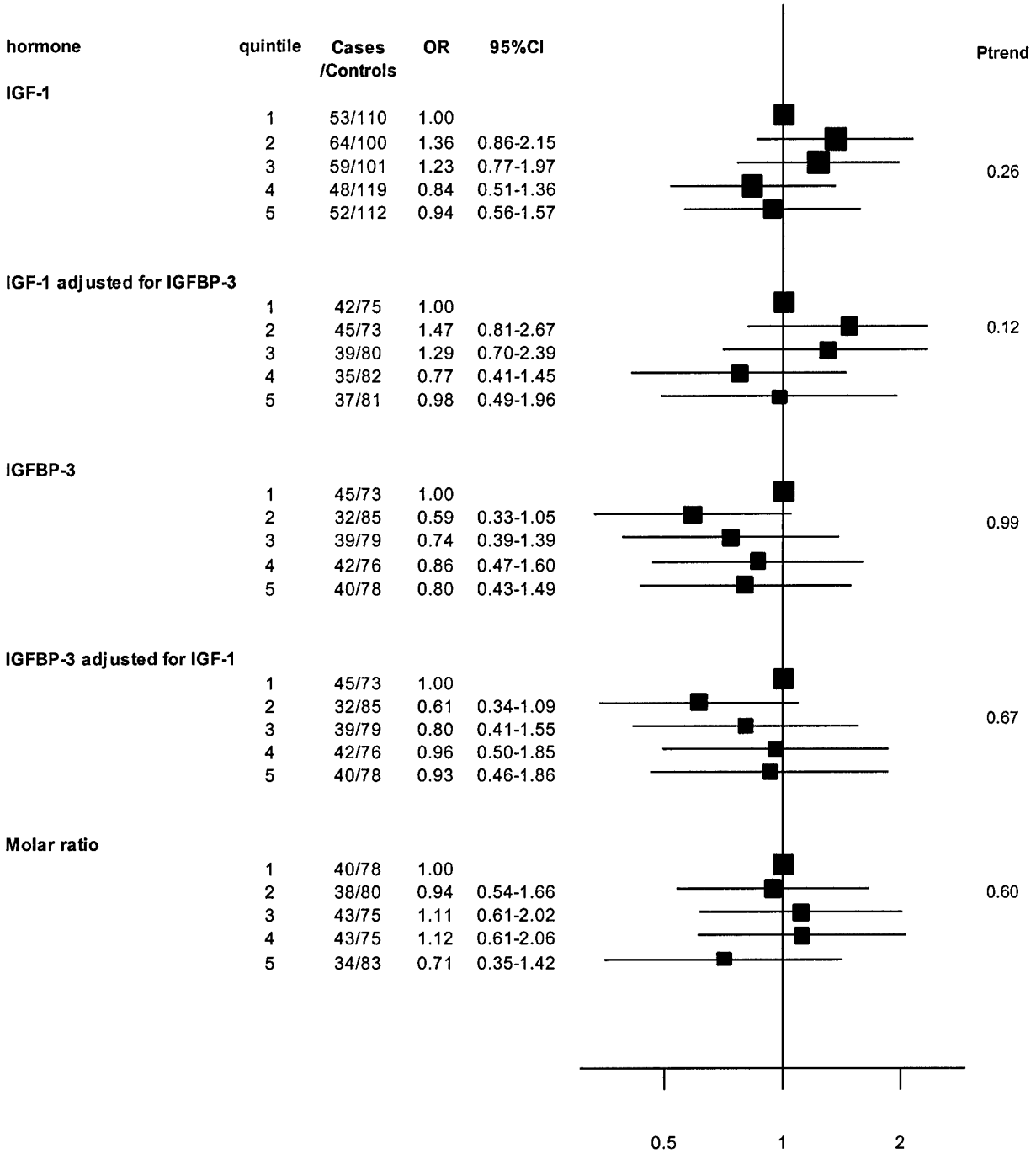

Figure 5. Relative risk of breast cancer among women older than 50 at diagnosis by quintiles of growth hormone levels

hormone	quintile	Cases /Controls	OR	95%CI	Ptrend
IGF-1					
	1	157/317	1.00		
	2	144/332	0.89	0.67-1.17	0.007
	3	153/319	0.99	0.75-1.30	
	4	166/315	1.11	0.84-1.47	
	5	188/287	1.41	1.06-1.87	
IGF-1 adjusted for IGFBP-3					
	1	120/231	1.00		0.46
	2	110/241	0.83	0.60-1.16	
	3	112/240	0.82	0.58-1.15	
	4	118/234	0.87	0.61-1.25	
	5	141/210	1.12	0.77-1.64	
IGFBP-3					
	1	114/239	1.00		0.005
	2	111/241	1.00	0.73-1.38	
	3	113/239	1.04	0.75-1.45	
	4	119/231	1.17	0.83-1.64	
	5	145/209	1.62	1.15-2.29	
IGFBP-3 adjusted for IGF-1					
	1	114/237	1.00		
	2	111/241	1.00	0.72-1.39	0.02
	3	113/239	1.04	0.73-1.48	
	4	119/231	1.18	0.81-1.72	
	5	144/208	1.64	1.08-2.47	
Molar ratio					
	1	129/223	1.00		
	2	116/235	0.82	0.60-1.13	0.90
	3	111/241	0.77	0.55-1.09	
	4	121/230	0.87	0.62-1.24	
	5	124/227	0.93	0.66-1.33	

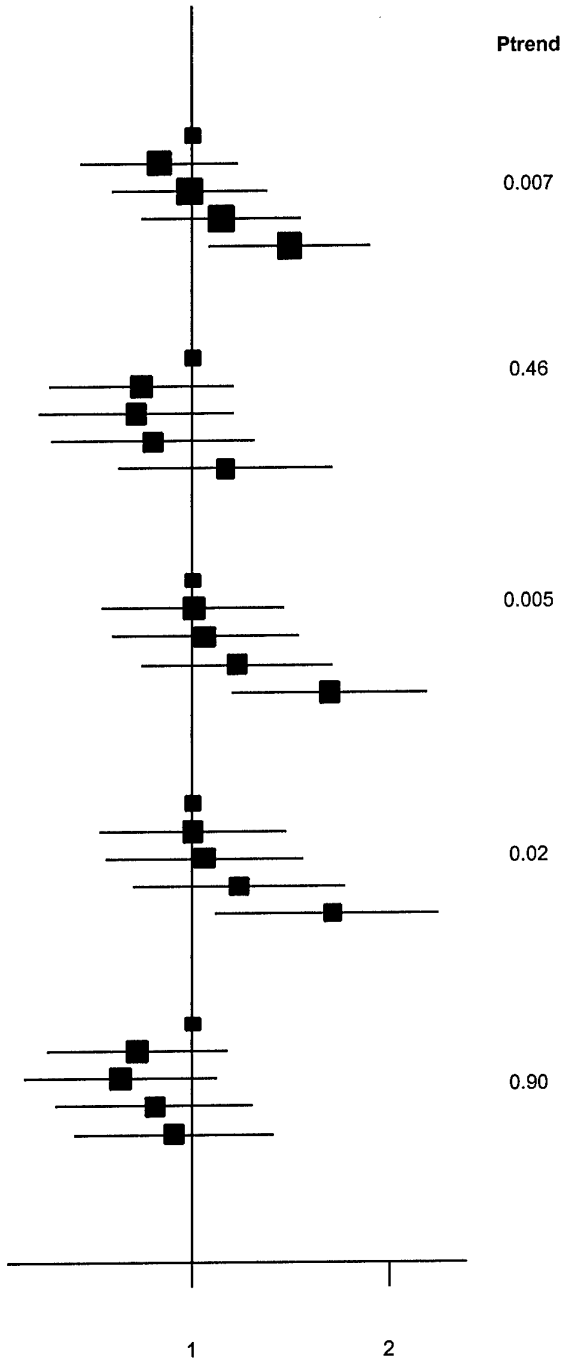

Figure 6. Relative risk of breast cancer among women younger than 60 at diagnosis by quintiles of growth hormone levels

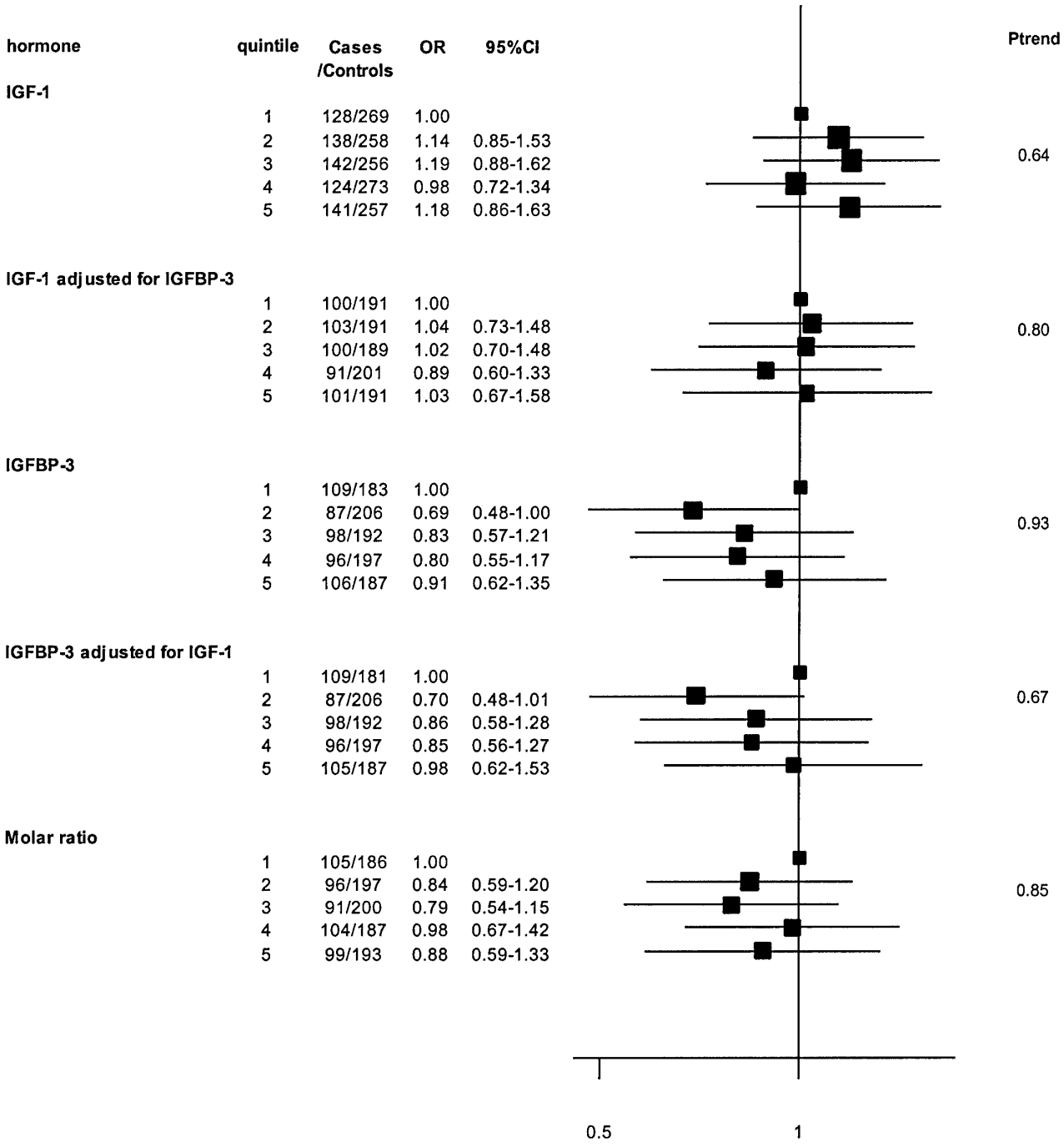

Figure 7. Relative risk of breast cancer among women older than 60 at diagnosis by quintiles of growth hormone levels

hormone	quintile	Cases /Controls	OR	95%CI	Ptrend
IGF-1					
	1	69/173	1.00		
	2	78/164	1.20	0.80-1.79	
	3	80/161	1.29	0.87-1.92	0.005
	4	91/153	1.53	1.04-2.25	
	5	93/148	1.69	1.12-2.56	
IGF-1 adjusted for IGFBP-3					
	1	54/123	1.00		
	2	57/122	0.91	0.56-1.48	0.55
	3	53/122	0.80	0.48-1.32	
	4	71/111	1.10	0.67-1.82	
	5	69/106	1.05	0.61-1.81	
IGFBP-3					
	1	49/129	1.00		0.0002
	2	56/123	1.26	0.80-2.00	
	3	58/118	1.39	0.87-2.21	
	4	63/116	1.65	1.01-2.70	
	5	78/99	2.48	1.52-4.05	
IGFBP-3 adjusted for IGF-1					
	1	49/129	1.00		
	2	56/123	1.27	0.79-2.05	0.002
	3	58/117	1.39	0.84-2.30	
	4	63/117	1.65	0.95-2.88	
	5	78/98	2.54	1.40-4.60	
Molar ratio					
	1	69/109	1.00		0.50
	2	58/119	0.75	0.48-1.18	
	3	54/124	0.67	0.42-1.06	
	4	63/115	0.84	0.52-1.34	
	5	60/117	0.78	0.48-1.27	

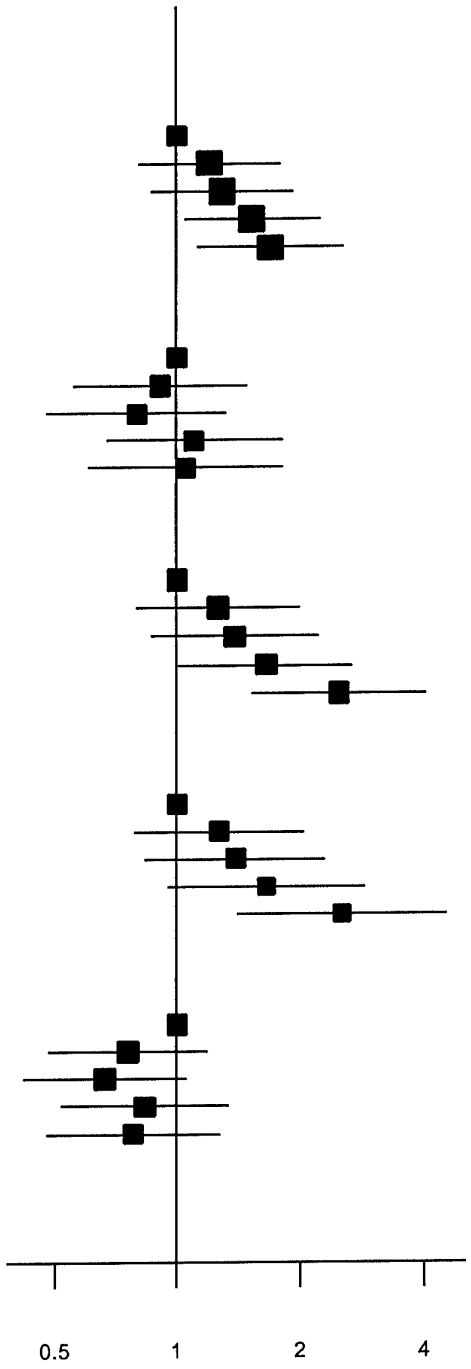

Table 1: Numbers of subjects genotyped for each of the 22 SNPs on 2342 subjects

SNP	Variables' names	N	N Missing	Frequency Missing
11GHR_M28462_174AG	G11GHRSM28462AG	2297	45	1.92
16GHR_M28466_748AC	G16GHRSM28466AC	2312	30	1.28
24IGF1_X57025_3340AG	G24IGF1SX57025AG	2314	28	1.20
28IGFBP1_M74587_187AG	G28IGFBP1SM74587AG	2295	47	2.01
30IGFBP1_M74587_5110CT	G30IGFBP1SM74587CT	2317	25	1.07
31IGFBP1_M74587_5179GA	G31IGFBP1SM74587GA	2322	20	0.85
33IGFBP3_M35878_5709GC	G33IGFBP3SM35878GC	2289	53	2.26
36IGFBP3_M35878_8291CT	G36IGFBP3SM35878CT	2322	20	0.85
38IGFBP3_M35878_9156AG	G38IGFBP3SM35878AG	2327	15	0.64
39IGFBP3_M35878_10049AAG	G39IGFBP3SM35878AAG	2311	31	1.32
40SST_J00306_1399TC	G40SSTSJ00306TC	2302	40	1.71
46SSTR3_M96738_889GA	G46SSTR3SM96738GA	2298	44	1.88
53SSTR5_D16827_192CA	G53SSTR5SD16827CA	2318	24	1.02
56GHRELIN_AC008116_48106AG	G56GHRELINSAC008116AG	2303	39	1.67
57GHRELIN_AC008116_48002AC	G57GHRELINSAC008116AC	2325	17	0.73
58GHRELIN_AF269558_3857AT	G58GHRELINSAF269558AT	2312	30	1.28
59GHRELIN_AF296558_4060GT	G59GHRELINSAF296558GT	2278	64	2.73
66GHRHR_AC005155_58474AG	G66GHRHRSAC005155AG	2329	13	0.56
69GHRHR_AC005155_63007GA	G69GHRHRSAC005155GA	2317	25	1.07
72GHRHR_AC005155_64092GC	G72GHRHRSAC005155GC	2318	24	1.02
73GHRH_AL031659_91261TC	G73GHRHSAL031659TC	2315	27	1.15
75SSTR4_D16826_900GT	G75SSTR4SD16826GT	2304	38	1.62

Table 2: For each SNP, numbers of observations, means of IGF-I by category of polymorphisms (homozygotes 1st allele, heterozygotes, homozygotes 2nd allele), p-values, R-square and R-square adjusted of different models with IGF-I as dependent variable (codominant model, dominant 1st allele, dominant 2nd allele) and average excess p-values of IGF-I

Gene	SNP	NObs	Mean1 (Nobs)	Mean2 (Nobs)	Mean3 (Nobs)	Codominant model			Dominant model 1st allele			Dominant model 2nd allele			Average Excess p-value
						Pvalue	Rsq	Rsq Adj	Pvalue	Rsq	Rsq Adj	Pvalue	Rsq	Rsq Adj	
GHR	G11GHRSM28462AG	2296	240.9 (198)	240.5 (922)	239.3 (1176)	0.70	0.00007	0.000000	0.69	0.00007	0.000000	0.85	0.00002	0.000000	0.67
	G16GHRSM28466AC	2311	239.8 (681)	240.4 (1093)	235.6 (537)	0.37	0.00034	0.000000	0.22	0.00063	0.000201	0.77	0.00004	0.000000	0.81
IGF1	G24IGF1SX57025AG	2313	239.2 (401)	238.7 (1114)	240.5 (798)	0.72	0.00006	0.000000	0.62	0.00010	0.000000	0.96	0.00000	0.000000	0.36
IGFBP1	G28IGFBP1SM74587AG	2294	240.0 (320)	238.6 (1098)	239.7 (876)	0.95	0.00000	0.000000	0.82	0.00002	0.000000	0.85	0.00002	0.000000	0.45
	G30IGFBP1SM74587CT	2316	239.0 (2134)	242.4 (174)	204.9 (8)	0.99	0.00000	0.000000	0.21	0.00069	0.000254	0.77	0.00004	0.000000	0.49
	G31IGFBP1SM74587GA	2321	239.1 (262)	237.2 (1042)	241.2 (1017)	0.40	0.00030	0.000000	0.26	0.00054	0.000113	0.99	0.00000	0.000000	0.20
IGFBP3	G33IGFBP3SM35878GC	2288	246.0 (99)	241.3 (762)	236.9 (1427)	0.11	0.00112	0.000687	0.13	0.00098	0.000546	0.34	0.00040	0.000000	0.05
	G36IGFBP3SM35878CT	2321	238.7 (2282)	279.2 (39)		0.001	0.00458	0.004151		0.00000	0.000000	0.001	0.00458	0.004151	<0.01
	G38IGFBP3SM35878AG	2326	239.0 (1506)	239.4 (734)	240.6 (86)	0.85	0.00002	0.000000	0.87	0.00001	0.000000	0.88	0.00001	0.000000	0.42
	G39IGFBP3SM35878AAG	2310	240.1 (1693)	236.1 (577)	234.3 (40)	0.25	0.00057	0.000140	0.70	0.00007	0.000000	0.25	0.00058	0.000143	0.88
SST	G40SSTSJ00306TC	2301	240.5 (1859)	232.8 (418)	246.7 (24)	0.15	0.00092	0.000488	0.63	0.00010	0.000000	0.09	0.00126	0.000825	0.06
SSTR3	G46SSTR3SM96738GA	2297	238.5 (1455)	240.3 (729)	243.8 (113)	0.42	0.00029	0.000000	0.52	0.00018	0.000000	0.48	0.00021	0.000000	0.23
SSTR5	G53SSTR5SD16827CA	2317	240.0 (2057)	233.7 (255)	187.1 (5)	0.11	0.00110	0.000667	0.13	0.00099	0.000559	0.16	0.00087	0.000439	0.05
GHRELIN	G56GHRELINSAC008116AG	2302	239.8 (801)	236.8 (1111)	243.2 (390)	0.71	0.00006	0.000000	0.23	0.00062	0.000187	0.69	0.00007	0.000000	0.35
	G57GHRELINSAC008116AC	2324	240.8 (1070)	237.2 (1012)	239.8 (242)	0.51	0.00019	0.000000	0.89	0.00001	0.000000	0.34	0.00040	0.000000	0.73
	G58GHRELINSAF269558AT	2311	239.1 (2027)	238.1 (273)	247.6 (11)	0.96	0.00000	0.000000	0.71	0.00006	0.000000	0.90	0.00001	0.000000	0.52
	G59GHRELINSAF296558GT	2277	242.4 (645)	237.4 (1080)	238.9 (552)	0.39	0.00032	0.000000	0.92	0.00001	0.000000	0.20	0.00071	0.000273	0.81
GHRHR	G66GHRHRSAC005155AG	2328	240.5 (1252)	238.8 (916)	230.9 (160)	0.19	0.00073	0.000305	0.16	0.00085	0.000423	0.36	0.00036	0.000000	0.91
	G69GHRHRSAC005155GA	2316	239.2 (1853)	239.6 (439)	222.3 (24)	0.72	0.00006	0.000000	0.28	0.00050	0.000069	0.91	0.00001	0.000000	0.63
	G72GHRHRSAC005155GC	2317	239.8 (1121)	239.3 (985)	235.4 (211)	0.54	0.00016	0.000000	0.46	0.00024	0.000000	0.71	0.00006	0.000000	0.74
GHRH	G73GHRHSAL031659TC	2314	238.8 (2218)	247.5 (96)		0.28	0.00051	0.000075		0.00000	0.000000	0.28	0.00051	0.000075	0.11
SSTR4	G75SSTR4SD16826GT	2303	240.4 (359)	241.1 (1094)	236.0 (850)	0.22	0.00065	0.000213	0.14	0.00097	0.000531	0.73	0.00005	0.000000	0.90

Table 3: For each SNP, numbers of observations, means of IGFBP3 by category of polymorphisms (homozygotes 1st allele, heterozygotes, homozygotes 2nd allele), p-values, R-square and R-square adjusted of different models with IGFBP3 as dependent variable (codominant model, dominant 1st allele, dominant 2nd allele) and average excess p-values of IGFBP3

Gene	SNP	NObs	Mean1 (Nobs)	Mean2 (Nobs)	Mean3 (Nobs)	Codominant model			Dominant model 1st allele			Dominant model 2nd allele			Average Excess p-value
						Pvalue	Rsq	Rsq Adj	Pvalue	Rsq	Rsq Adj	Pvalue	Rsq	Rsq Adj	
GHR	G11GHRSM28462AG	2292	2939 (196)	3003 (920)	2956 (1176)	0.54	0.00017	0.000000	0.23	0.00063	0.000192	0.47	0.00023	0.000000	0.73
	G16GHRSM28466AC	2308	2953 (680)	2988 (1092)	2964 (536)	0.73	0.00005	0.000000	0.75	0.00004	0.000000	0.40	0.00031	0.000000	0.35
IGF1	G24IGF1SX57025AG	2309	2966 (399)	2956 (1113)	3005 (797)	0.25	0.00058	0.000142	0.14	0.00096	0.000524	0.79	0.00003	0.000000	0.08
IGFBP1	G28IGFBP1SM74587AG	2290	2949 (318)	2991 (1096)	2965 (876)	0.97	0.00000	0.000000	0.57	0.00014	0.000000	0.47	0.00023	0.000000	0.51
	G30IGFBP1SM74587CT	2312	2967 (2130)	3029 (174)	3268 (8)	0.14	0.00096	0.000530	0.24	0.00061	0.000176	0.18	0.00077	0.000334	0.06
	G31IGFBP1SM74587GA	2317	2941 (260)	2977 (1041)	2978 (1016)	0.56	0.00015	0.000000	0.78	0.00003	0.000000	0.43	0.00027	0.000000	0.30
IGFBP3	G33IGFBP3SM35878GC	2284	2741 (99)	2928 (760)	3014 (1425)	<.0001	0.00758	0.007146	0.0004	0.00545	0.005010	0.001	0.00492	0.004487	<0.001
	G36IGFBP3SM35878CT	2317	2977 (2278)	2777 (39)		0.08	0.00134	0.000905		0.00000		0.08	0.00134	0.000905	0.04
	G38IGFBP3SM35878AG	2322	2979 (1505)	2954 (731)	3020 (86)	0.78	0.00003	0.000000	0.53	0.00017	0.000000	0.57	0.00014	0.000000	0.61
	G39IGFBP3SM35878AAG	2306	2962 (1691)	3002 (575)	3044 (40)	0.18	0.00078	0.000344	0.52	0.00018	0.000000	0.20	0.00072	0.000285	0.09
SST	G40SSTSJ00306TC	2297	2967 (1856)	2998 (417)	2880 (24)	0.65	0.00009	0.000000	0.52	0.00018	0.000000	0.51	0.00019	0.000000	0.32
SSTR3	G46SSTR3SM96738GA	2293	2979 (1453)	2966 (728)	2959 (112)	0.65	0.00009	0.000000	0.83	0.00002	0.000000	0.65	0.00009	0.000000	0.68
SSTR5	G53SSTR5SD16827CA	2313	2974 (2053)	2977 (255)	2737 (5)	0.88	0.00001	0.000000	0.45	0.00025	0.000000	0.97	0.00000	0.000000	0.55
GHRELIN	G56GHRELINSAC008116AG	2298	2998 (800)	2962 (1109)	2976 (389)	0.46	0.00024	0.000000	0.98	0.00000	0.000000	0.29	0.00049	0.000053	0.73
	G57GHRELINSAC008116AC	2320	2975 (1067)	2952 (1010)	3064 (243)	0.35	0.00038	0.000000	0.04	0.00188	0.001452	0.97	0.00000	0.000000	0.18
	G58GHRELINSAF269558AT	2307	2968 (2024)	3002 (272)	3011 (11)	0.44	0.00026	0.000000	0.85	0.00002	0.000000	0.44	0.00026	0.000000	0.23
	G59GHRELINSAF296558GT	2273	3021 (645)	2980 (1078)	2916 (550)	0.01	0.00287	0.002426	0.02	0.00235	0.001910	0.06	0.00159	0.001152	0.02
GHRHR	G66GHRHRSAC005155AG	2324	2970 (1250)	2958 (916)	3078 (158)	0.34	0.00039	0.000000	0.05	0.00164	0.001214	0.85	0.00002	0.000000	0.18
	G69GHRHRSAC005155GA	2312	2970 (1850)	2989 (438)	2912 (24)	0.78	0.00003	0.000000	0.67	0.00008	0.000000	0.68	0.00007	0.000000	0.41
	G72GHRHRSAC005155GC	2313	2964 (1120)	2966 (984)	3052 (209)	0.22	0.00064	0.000208	0.09	0.00127	0.000833	0.55	0.00015	0.000000	0.11
GHRH	G73GHRHSAL031659TC	2310	2970 (2214)	3006 (96)		0.62	0.00010	0.000000		0.00000		0.62	0.00010	0.000000	0.31
SSTR4	G75SSTR4SD16826GT	2299	2978 (358)	2978 (1092)	2965 (849)	0.71	0.00006	0.000000	0.67	0.00008	0.000000	0.89	0.00001	0.000000	0.66

Table 4: Number of SNPs per gene, R-square adjusted of full rank haplotype models and results of stepwise regression models

Gene	Number of SNPs	R^2adj of full rank ("maximum") haplotype model (Rsq)		Result from stepwise regression: Nr of SNP loci showing effects / model p-value / model R^2adj (Rsq)	
		IGF-1	IGFBP-3	IGF-1	IGFBP-3
GHR	2	0.0000 (.0006)	0.0004 (.002)	/	/
IGF1	1	0.0000 (.0001)	0.0005 (.001)	/	/
IGFBP1	3	0.0000 (.002)	0.0004 (.002)	/	/
IGFBP3	4	0.003 (.006)	0.007 (.0103)	1 / p=.001 / R^2=(.0005).004	1 / p=.001 / R^2=(.008).007
SST	1	0.0008 (.001)	0.0000 (.0005)	/	/
SSTR3	1	0.0000 (.0003)	0.0000 (.0001)	/	/
SSTR5	1	0.0008 (.002)	0.0000 (.0001)	/	/
GHRELIN	4	0.0000 (.002)	0.0035 (.007)	2 / p=.02 / R^2=(.008).004	2 / p=.01 / R^2=(.005).003
GHRHR	3	0.0000 (.002)	0.0000 (.002)	/	/
GHRH	1	0.0001 (.0005)	0.0000 (.0001)	/	/
SSTR4	1	0.0005 (.001)	0.0000 (.0001)	/	/

Codominant model

Table 5: For each SNP, numbers of cases and controls by category of polymorphisms (homozygotes 1st allele, heterozygotes, homozygotes 2nd allele), hazard ratios, confidence intervals and p-values associated, means of IGF-I and IGFBP3 and p-values of the mean's tests

Gene	Variable	cases	controls	n	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
GHR	G11	779	1507	2286	.	.	.	0.6952	.	0.8366	.	0.2887
	G111	61	138	199	.	.	.	.	240.613	.	2940.60	.
	G112	322	601	923	1.207	0.869	1.677	0.2620	240.995	.	3001.12	.
	G113	396	768	1164	1.158	0.837	1.603	0.3753	239.023	.	2957.27	.
GHR	G16	774	1517	2291	.	.	.	0.9917	.	0.4771	.	0.6211
	G161	219	454	673	.	.	.	.	239.862	.	2953.04	.
	G162	387	708	1095	1.139	0.925	1.402	0.2202	240.740	.	2986.75	.
	G163	168	355	523	0.982	0.766	1.259	0.8877	235.851	.	2976.15	.
IGF1	G24	774	1521	2295	.	.	.	0.2417	.	0.5469	.	0.2918
	G241	131	271	402	.	.	.	.	238.896	.	2982.14	.
	G242	364	749	1113	0.999	0.783	1.273	0.9913	238.215	.	2955.57	.
	G243	279	501	780	1.133	0.879	1.460	0.3357	242.073	.	3007.18	.
IGFBP1	G28	770	1497	2267	.	.	.	0.7454	.	0.8628	.	0.4479
	G281	114	208	322	.	.	.	.	240.002	.	2946.05	.
	G282	353	734	1087	0.871	0.671	1.131	0.2992	238.277	.	2993.69	.
	G283	303	555	858	0.981	0.751	1.281	0.8865	240.044	.	2961.21	.
IGFBP1	G30	776	1524	2300	.	.	.	0.7178	.	0.4384	.	0.2107
	G301	712	1407	2119	.	.	.	.	239.301	.	2967.49	.
	G302	62	111	173	1.110	0.799	1.543	0.5330	240.550	.	3041.25	.
	G303	2	6	8	0.667	0.135	3.303	0.6197	204.883	.	3267.95	.
IGFBP1	G31	780	1533	2313	.	.	.	0.7641	.	0.3612	.	0.6120
	G311	89	175	264	.	.	.	.	239.072	.	2934.10	.
	G312	345	693	1038	0.977	0.733	1.303	0.8739	236.931	.	2979.98	.
	G313	346	665	1011	1.019	0.762	1.362	0.8988	241.774	.	2980.28	.

Codominant model

Gene	Variable	cases	controls	n	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
IGFBP3	G33	767	1489	2256	.	.	.	0.9793	.	0.2275	.	<.0001
	G331	38	59	97	.	.	.	.	246.473	.	2708.65	.
	G332	247	506	753	0.763	0.493	1.183	0.2270	241.850	.	2924.81	.
	G333	482	924	1406	0.824	0.540	1.258	0.3702	236.949	.	3022.11	.
IGFBP3	G36	776	1529	2305	.	.	.	0.3330	.	0.0019	.	0.0584
	G361	766	1501	2267	.	.	.	.	238.807	.	2977.93	.
	G362	10	28	38	0.700	0.340	1.442	0.3330	277.659	.	2759.58	.
	G363	.	.	.	.	.	.	.	.	.	.	.
IGFBP3	G38	782	1540	2322	.	.	.	0.1892	.	0.9739	.	0.7130
	G381	521	980	1501	.	.	.	.	239.216	.	2980.09	.
	G382	234	501	735	0.880	0.727	1.065	0.1900	239.219	.	2957.79	.
	G383	27	59	86	0.871	0.549	1.383	0.5588	241.154	.	3006.51	.
IGFBP3	G39	778	1520	2298	.	.	.	0.5523	.	0.4213	.	0.3914
	G391	563	1115	1678	.	.	.	.	240.555	.	2964.44	.
	G392	201	379	580	1.059	0.864	1.299	0.5787	235.856	.	3009.31	.
	G393	14	26	40	1.092	0.569	2.095	0.7916	235.352	.	3014.71	.
SST	G40	775	1510	2285	.	.	.	0.0454	.	0.1040	.	0.4577
	G401	608	1241	1849	.	.	.	.	240.855	.	2965.64	.
	G402	158	255	413	1.251	1.001	1.562	0.0487	232.159	.	3006.97	.
	G403	9	14	23	1.311	0.565	3.043	0.5283	246.274	.	2876.80	.
SSTR3	G46	772	1501	2273	.	.	.	0.8182	.	0.6986	.	0.9457
	G461	491	945	1436	.	.	.	.	238.638	.	2976.59	.
	G462	243	483	726	0.970	0.803	1.172	0.7527	240.654	.	2965.80	.
	G463	38	73	111	0.996	0.662	1.498	0.9829	243.924	.	2974.45	.

Codominant model

Gene	Variable	cases	controls	n	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
SSTR5	G53	769	1518	2287	.	.	.	0.3062	.	0.1509	.	0.7075
	G531	676	1358	2034	.	.	.	.	239.961	.	2974.45	.
	G532	92	156	248	1.192	0.906	1.568	0.2084	233.738	.	2991.32	.
	G533	1	4	5	0.501	0.056	4.477	0.5364	187.100	.	2736.98	.
GHRELIN	G56	776	1512	2288	.	.	.	0.7585	.	0.2896	.	0.3989
	G561	272	523	795	.	.	.	.	240.740	.	3006.25	.
	G562	376	729	1105	0.994	0.821	1.203	0.9497	236.573	.	2965.22	.
	G563	128	260	388	0.956	0.739	1.238	0.7332	242.827	.	2961.63	.
GHRELIN	G57	780	1535	2315	.	.	.	0.6534	.	0.6764	.	0.0797
	G571	361	696	1057	.	.	.	.	240.200	.	2972.50	.
	G572	340	676	1016	0.974	0.810	1.172	0.7830	237.632	.	2955.66	.
	G573	79	163	242	0.937	0.694	1.265	0.6693	241.301	.	3069.31	.
GHRELIN	G58	773	1518	2291	.	.	.	0.0270	.	0.8780	.	0.6936
	G581	662	1347	2009	.	.	.	.	239.290	.	2969.32	.
	G582	106	165	271	1.314	1.011	1.708	0.0408	237.550	.	3007.82	.
	G583	5	6	11	1.711	0.522	5.611	0.3753	247.643	.	3011.32	.
GHRELIN	G59	759	1469	2228	.	.	.	0.4480	.	0.3383	.	0.0190
	G591	217	419	636	.	.	.	.	243.175	.	3024.12	.
	G592	370	686	1056	1.037	0.844	1.274	0.7309	237.800	.	2985.13	.
	G593	172	364	536	0.906	0.712	1.153	0.4227	238.166	.	2909.03	.
GHRHR	G66	782	1541	2323	.	.	.	0.2385	.	0.1942	.	0.1629
	G661	433	822	1255	.	.	.	.	241.186	.	2975.90	.
	G662	302	608	910	0.943	0.788	1.128	0.5178	238.077	.	2954.66	.
	G663	47	111	158	0.808	0.565	1.154	0.2403	230.077	.	3071.33	.

Codominant model

Gene	Variable	cases	controls	n	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
GHRHR	G69	775	1525	2300	.	.	.	0.2928	.	0.6572	.	0.9420
	G691	608	1220	1828	.	.	.	.	239.143	.	2971.99	.
	G692	157	292	449	1.078	0.870	1.336	0.4917	240.066	.	2981.98	.
	G693	10	13	23	1.559	0.683	3.559	0.2916	225.122	.	2941.37	.
GHRHR	G72	775	1526	2301	.	.	.	0.0705	.	0.6981	.	0.2317
	G721	392	723	1115	.	.	.	.	240.186	.	2969.26	.
	G722	322	651	973	0.910	0.758	1.092	0.3091	239.523	.	2960.21	.
	G723	61	152	213	0.753	0.549	1.034	0.0792	235.330	.	3050.88	.
GHRH	G73	776	1522	2298	.	.	.	0.5009	.	0.2513	.	0.5514
	G731	741	1462	2203	.	.	.	.	238.711	.	2968.93	.
	G732	35	60	95	1.160	0.753	1.787	0.5009	247.932	.	3012.96	.
	G733	.	.	.	.	.	.	.	.	.	.	.
SSTR4	G75	765	1501	2266	.	.	.	0.7021	.	0.3180	.	0.9147
	G751	112	242	354	.	.	.	.	240.398	.	2987.89	.
	G752	377	710	1087	1.172	0.905	1.517	0.2283	241.032	.	2972.68	.
	G753	276	549	825	1.105	0.841	1.451	0.4742	235.834	.	2969.07	.

Dominant model 1st allele

Table 6: For each SNP, numbers of cases and controls by category of polymorphisms (homozygotes 1st allele and heterozygotes, homozygotes 2nd allele), hazard ratios, confidence intervals and p-values associated, means of IGF-I and IGFBP3 and p-values of the mean's tests

Gene	Variable	cases	controls	n	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
GHR	G11	779	1507	2286	.	.	.	0.9282	.	0.5525	.	0.2580
	G111	396	768	1164	.	.	.	.	239.023	.	2957.27	.
	G112	383	739	1122	1.008	0.845	1.203	0.9282	240.927	.	2990.49	.
GHR	G16	774	1517	2291	.	.	.	0.3628	.	0.2324	.	0.9495
	G161	168	355	523	.	.	.	.	235.851	.	2976.15	.
	G162	606	1162	1768	1.103	0.893	1.364	0.3628	240.406	.	2973.92	.
IGF1	G24	774	1521	2295	.	.	.	0.1714	.	0.2766	.	0.1524
	G241	279	501	780	.	.	.	.	242.073	.	3007.18	.
	G242	495	1020	1515	0.882	0.737	1.056	0.1714	238.396	.	2962.60	.
IGFBP1	G28	770	1497	2267	.	.	.	0.3432	.	0.6802	.	0.4825
	G281	303	555	858	.	.	.	.	240.044	.	2961.21	.
	G282	467	942	1409	0.917	0.767	1.097	0.3432	238.671	.	2982.83	.
IGFBP1	G30	776	1524	2300	.	.	.	0.6197	.	0.2048	.	0.2399
	G301	2	6	8	.	.	.	.	204.883	.	3267.95	.
	G302	774	1518	2292	1.500	0.303	7.429	0.6197	239.396	.	2973.08	.
IGFBP1	G31	780	1533	2313	.	.	.	0.6754	.	0.1711	.	0.7475
	G311	346	665	1011	.	.	.	.	241.774	.	2980.28	.
	G312	434	868	1302	0.963	0.808	1.148	0.6754	237.365	.	2970.71	.
IGFBP3	G33	767	1489	2256	.	.	.	0.6435	.	0.1036	.	<.0001
	G331	482	924	1406	.	.	.	.	236.949	.	3022.11	.
	G332	285	565	850	0.958	0.798	1.149	0.6435	242.378	.	2900.06	.

Dominant model 1st allele

Gene	Variable	cases	controls	n	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
IGFBP3	G38	782	1540	2322	.	.	.	0.6735	.	0.8182	.	0.6642
	G381	27	59	86	.	.	.	.	241.154	.	3006.51	.
	G382	755	1481	2236	1.104	0.698	1.745	0.6735	239.217	.	2972.78	.
IGFBP3	G39	778	1520	2298	.	.	.	0.8210	.	0.7435	.	0.7287
	G391	14	26	40	.	.	.	.	235.352	.	3014.71	.
	G392	764	1494	2258	0.928	0.485	1.776	0.8210	239.349	.	2975.93	.
SST	G40	775	1510	2285	.	.	.	0.6075	.	0.6630	.	0.5165
	G401	9	14	23	.	.	.	.	246.274	.	2876.80	.
	G402	766	1496	2262	0.803	0.347	1.858	0.6075	239.265	.	2973.18	.
SSTR3	G46	772	1501	2273	.	.	.	0.9727	.	0.5358	.	0.9830
	G461	38	73	111	.	.	.	.	243.924	.	2974.45	.
	G462	734	1428	2162	0.993	0.664	1.485	0.9727	239.315	.	2972.97	.
SSTR5	G53	769	1518	2287	.	.	.	0.5364	.	0.1277	.	0.4513
	G531	1	4	5	.	.	.	.	187.100	.	2736.98	.
	G532	768	1514	2282	1.995	0.223	17.821	0.5364	239.283	.	2976.29	.
GHRELIN	G56	776	1512	2288	.	.	.	0.7266	.	0.2914	.	0.5983
	G561	128	260	388	.	.	.	.	242.827	.	2961.63	.
	G562	648	1252	1900	1.042	0.827	1.312	0.7266	238.316	.	2982.39	.
GHRELIN	G57	780	1535	2315	.	.	.	0.7192	.	0.6519	.	0.0290
	G571	79	163	242	.	.	.	.	241.301	.	3069.31	.
	G572	701	1372	2073	1.054	0.792	1.402	0.7192	238.943	.	2964.25	.
GHRELIN	G58	773	1518	2291	.	.	.	0.3988	.	0.7114	.	0.8611
	G581	5	6	11	.	.	.	.	247.643	.	3011.32	.
	G582	768	1512	2280	0.600	0.183	1.966	0.3988	239.083	.	2973.88	.

Dominant model 1st allele

Gene	Variable	cases	controls	n	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
GHRELIN	G59	759	1469	2228	.	.	.	0.2408	.	0.6613	.	0.0096
	G591	172	364	536	.	.	.	.	238.166	.	2909.03	.
	G592	587	1105	1692	1.129	0.922	1.382	0.2408	239.820	.	2999.77	.
GHRHR	G66	782	1541	2323	.	.	.	0.2884	.	0.1205	.	0.0758
	G661	47	111	158	.	.	.	.	230.077	.	3071.33	.
	G662	735	1430	2165	1.208	0.852	1.712	0.2884	239.880	.	2966.97	.
GHRHR	G69	775	1525	2300	.	.	.	0.3057	.	0.3750	.	0.8263
	G691	10	13	23	.	.	.	.	225.122	.	2941.37	.
	G692	765	1512	2277	0.650	0.285	1.482	0.3057	239.325	.	2973.96	.
GHRHR	G72	775	1526	2301	.	.	.	0.1222	.	0.4096	.	0.0920
	G721	61	152	213	.	.	.	.	235.330	.	3050.88	.
	G722	714	1374	2088	1.273	0.937	1.728	0.1222	239.877	.	2965.05	.
SSTR4	G75	765	1501	2266	.	.	.	0.7927	.	0.1316	.	0.8127
	G751	276	549	825	.	.	.	.	235.834	.	2969.07	.
	G752	489	952	1441	1.025	0.854	1.230	0.7927	240.876	.	2976.42	.

Dominant model 2nd allele

Table 7: For each SNP, numbers of cases and controls by category of polymorphisms (homozygotes 1st allele, heterozygotes and homozygotes 2nd allele), hazard ratios, confidence intervals and p-values associated, means of IGF-I and IGFBP3 and p-values of the mean's tests

Gene	Variable	cases	controls	n	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
GHR	G11	779	1507	2286	.	.	.	0.2990	.	0.8995	.	0.4911
	G111	61	138	199	.	.	.	.	240.613	.	2940.60	.
	G112	718	1369	2087	1.181	0.863	1.615	0.2990	239.896	.	2976.65	.
GHR	G16	774	1517	2291	.	.	.	0.4107	.	0.8412	.	0.3501
	G161	219	454	673	.	.	.	.	239.862	.	2953.04	.
	G162	555	1063	1618	1.085	0.893	1.318	0.4107	239.158	.	2983.32	.
IGF1	G24	774	1521	2295	.	.	.	0.6586	.	0.8291	.	0.8917
	G241	131	271	402	.	.	.	.	238.896	.	2982.14	.
	G242	643	1250	1893	1.053	0.838	1.323	0.6586	239.805	.	2976.84	.
IGFBP1	G28	770	1497	2267	.	.	.	0.4991	.	0.8378	.	0.4367
	G281	114	208	322	.	.	.	.	240.002	.	2946.05	.
	G282	656	1289	1945	0.919	0.718	1.175	0.4991	239.056	.	2979.35	.
IGFBP1	G30	776	1524	2300	.	.	.	0.6188	.	0.9561	.	0.1268
	G301	712	1407	2119	.	.	.	.	239.301	.	2967.49	.
	G302	64	117	181	1.085	0.787	1.497	0.6188	238.974	.	3051.27	.
IGFBP1	G31	780	1533	2313	.	.	.	0.9814	.	0.9608	.	0.3217
	G311	89	175	264	.	.	.	.	239.072	.	2934.10	.
	G312	691	1358	2049	0.997	0.758	1.311	0.9814	239.319	.	2980.12	.
IGFBP3	G33	767	1489	2256	.	.	.	0.3068	.	0.3265	.	0.0001
	G331	38	59	97	.	.	.	.	246.473	.	2708.65	.
	G332	729	1430	2159	0.804	0.529	1.222	0.3068	238.658	.	2988.18	.

Dominant model 2nd allele

Gene	Variable	cases	controls	n	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
IGFBP3	G36	776	1529	2305	.	.	.	0.3330	.	0.0019	.	0.0584
	G361	766	1501	2267	.	.	.	.	238.807	.	2977.93	.
	G362	10	28	38	0.700	0.340	1.442	0.3330	277.659	.	2759.58	.
IGFBP3	G38	782	1540	2322	.	.	.	0.1686	.	0.9507	.	0.5769
	G381	521	980	1501	.	.	.	.	239.216	.	2980.09	.
	G382	261	560	821	0.879	0.732	1.056	0.1686	239.422	.	2962.92	.
IGFBP3	G39	778	1520	2298	.	.	.	0.5522	.	0.1887	.	0.1710
	G391	563	1115	1678	.	.	.	.	240.555	.	2964.44	.
	G392	215	405	620	1.062	0.871	1.294	0.5522	235.823	.	3009.66	.
SST	G40	775	1510	2285	.	.	.	0.0421	.	0.0516	.	0.3626
	G401	608	1241	1849	.	.	.	.	240.855	.	2965.64	.
	G402	167	269	436	1.254	1.008	1.559	0.0421	232.903	.	3000.07	.
SSTR3	G46	772	1501	2273	.	.	.	0.7695	.	0.4618	.	0.7546
	G461	491	945	1436	.	.	.	.	238.638	.	2976.59	.
	G462	281	556	837	0.973	0.811	1.167	0.7695	241.088	.	2966.93	.
SSTR5	G53	769	1518	2287	.	.	.	0.2500	.	0.1614	.	0.8024
	G531	676	1358	2034	.	.	.	.	239.961	.	2974.45	.
	G532	93	160	253	1.173	0.894	1.538	0.2500	232.816	.	2986.29	.
GHRELIN	G56	776	1512	2288	.	.	.	0.8648	.	0.4501	.	0.1760
	G561	272	523	795	.	.	.	.	240.740	.	3006.25	.
	G562	504	989	1493	0.984	0.821	1.181	0.8648	238.196	.	2964.29	.
GHRELIN	G57	780	1535	2315	.	.	.	0.7087	.	0.5611	.	0.8634
	G571	361	696	1057	.	.	.	.	240.200	.	2972.50	.
	G572	419	839	1258	0.967	0.811	1.153	0.7087	238.336	.	2977.60	.

Dominant model 2nd allele

Gene	Variable	cases	controls	n	HazardRatio	HRLowerCL	HRUpperCL	ProbChiSq	IGF1 mean	Probf	IGFBP3 mean	Probf
GHRELIN	G58	773	1518	2291	.	.	.	0.0301	.	0.7821	.	0.3923
	G581	662	1347	2009	.	.	.	.	239.290	.	2969.32	.
	G582	111	171	282	1.329	1.028	1.718	0.0301	237.943	.	3007.95	.
GHRELIN	G59	759	1469	2228	.	.	.	0.9215	.	0.1416	.	0.0514
	G591	217	419	636	.	.	.	.	243.175	.	3024.12	.
	G592	542	1050	1592	0.990	0.817	1.201	0.9215	237.923	.	2959.52	.
GHRHR	G66	782	1541	2323	.	.	.	0.3530	.	0.1785	.	0.8858
	G661	433	822	1255	.	.	.	.	241.186	.	2975.90	.
	G662	349	719	1068	0.922	0.777	1.094	0.3530	236.891	.	2971.67	.
GHRHR	G69	775	1525	2300	.	.	.	0.3786	.	0.9609	.	0.8272
	G691	608	1220	1828	.	.	.	.	239.143	.	2971.99	.
	G692	167	305	472	1.099	0.891	1.355	0.3786	239.336	.	2980.00	.
GHRHR	G72	775	1526	2301	.	.	.	0.1422	.	0.6575	.	0.8091
	G721	392	723	1115	.	.	.	.	240.186	.	2969.26	.
	G722	383	803	1186	0.879	0.739	1.044	0.1422	238.768	.	2976.36	.
GHRH	G73	776	1522	2298	.	.	.	0.5009	.	0.2513	.	0.5514
	G731	741	1462	2203	.	.	.	.	238.711	.	2968.93	.
	G732	35	60	95	1.160	0.753	1.787	0.5009	247.932	.	3012.96	.
SSTR4	G75	765	1501	2266	.	.	.	0.2827	.	0.7164	.	0.6834
	G751	112	242	354	.	.	.	.	240.398	.	2987.89	.
	G752	653	1259	1912	1.145	0.894	1.466	0.2827	238.788	.	2971.12	.